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10/715,220	11/17/2003	Aristo Vojdani	IMSCI.009C2	5017

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EXAMINER	
SWITZER, JULIET CAROLINE	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/715,220	VOJDANI, ARISTO	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Regarding the 09/620375 application, Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

This application is claiming the benefit of prior-filed nonprovisional application No. 06/620375 under 35 U.S.C. 120, 121, or 365(c). Copendency between the current application and the prior application is required. Since the applications are not copending, the benefit claim to the prior-filed nonprovisional application is improper. Applicant is required to delete the reference to the prior-filed application from the first sentence(s) of the specification, or the application data sheet, depending on where the reference was originally submitted, unless applicant can establish copendency between the applications.

2. Further, applicant is requested to amend the first line of the specification to indicate that co-pending 09/620375 has issued as US 6815161.

Information Disclosure Statement

3. The IDS filed 11/17/03 has been considered. A signed copy of the 1449 is enclosed with this office action.

4. All of the references that are cited in this office action are included in the IDS, except for the single reference listed on the enclosed notice of references cited and included with this office action.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-3 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6492113. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claim of the issued patent anticipates the instantly claimed invention. The primers used in the claimed method,

namely instant SEQ ID NO: 8 and SEQ ID NO: 9 inherently detect *M. fermentans*, see issued patent Col. 8, Example 5.

7. Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 6515161. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the instant claims is anticipated by at least one of the issued claims.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-4 and 6-14 are rejected under 35 U.S.C. 102(a) as being anticipated by Choppa et al. (Molecular and Cellular Probes (1998), 12, 301-308).

It is noted that the authorship of the Choppa et al. reference is distinct from the inventorship of the instant application and that this rejection may be overcome by the filing of a 132 Katz-type declaration.

Choppa et al. teach a method which uses mutliplex PCR for the detection of *Mycoplasma fermentans*, *M. hominis* and *M. penetrans* in peripheral blood mononuclear cells of patients with chronic fatigue syndrome (see methods p. 302). The primers used in the multiplex PCR are

given on p. 304 and are identical to SEQUENCE ID NO: 3-8 of the instant application. Choppa et al. report that mycoplasmas were found at a significantly higher rate in CFS individuals over healthy controls (p. 307). Further, Choppa et al. suggest that such a detection technique would have a diagnostic value since there is a need for rapid reliable diagnostic procedures (p. 307). Thus, Choppa teach a method which comprises the steps of isolating PBMC from an individual and detecting the presence of at least on mycoplasma species in said PBMC, wherein the presence of at least one of said species indicates an increased likelihood of the presence of CFS.

10. Claims 1-3, 5-7, 10 and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by Vojdani et al. (FEMS Immunology and Medical Microbiology 22 (1998) 355-365).

It is noted that the authorship of the Vojdani et al. reference is distinct from the inventorship of the instant application and that this rejection may be overcome by the filing of a 132 Katz-type declaration.

Vojadani et al. teach a method which employs a set of genus specific primers to detect mycoplasma in the PMBC samples of patients with CFS. Vojdani et al. further teach a method which uses PCR for the detection of *M. fermentans* in peripheral blood mononuclear cells of patients with chronic fatigue syndrome. The primers used by Vojdani et al to amplify *M. fermentans* consists of SEQUENCE ID NO: 3 and 4 of the instant application (p. 358). *M. fermentans* was observed in 34% of patients with CFS as opposed to 8% of the control group (Table 1). Vojadani et al. observe that some samples were positive for mycoplasma genus but not for *M. fermentans*, indicating the simultaneous detection of more than one mycoplasma

species. Thus, Vojadani et al. teach a method which comprises the steps of isolating PBMC from an individual and detecting the presence of at least on mycoplasma species in said PBMC, wherein the presence of at least one of said species indicates an increased likelihood of the presence of CFS.

11. Claims 1, 2, 3, 4, 10, 11, 12, 13, 14 are rejected under 35 U.S.C. 102(a) as being anticipated by Vojdani et al. (October 1998, Fourth International AACFS Research & Clinical Conference on CFIDS, Abstract entitled Multiplex PCR for the Detection of Mycoplasma fermentans, M. hominis, and M. penetrans in patients with Chronic Fatigue, Fibromyalgia, Rheumatoid Arthritis, and Gulf War Syndrome).

Vojdani et al. teach a method which uses mutliplex PCR for the simultaneous detection of *Mycoplasma fermentans*, *M. hominis* and *M. penetrans* in peripheral blood mononuclear cells of patients with chronic fatigue syndrome, fibromyalgia, and rheumatoid arthritis. Vojdani et al. report that mycoplasmas were found at a significantly higher rate in patients with illness over healthy controls. Further, Vojdani et al. suggest that such a detection technique would have a diagnostic value since there is a need for rapid reliable diagnostic procedures. Thus, Vojdani teach a method which comprises the steps of isolating PBMC from an individual and detecting the presence of at least on mycoplasma species in said PBMC, wherein the presence of at least one of said species indicates an increased likelihood of the presence of CFS.

12. Claims 1-2, 5, 10, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Nicolson et al. (International Journal of Occupational Medicine, Immunology, and Toxicology, Volume 5, No. 1, 1996).

Nicolson et al. (1996) teach a method for detecting mycoplasma in the leukocytes of patients with Gulf War Illness (GWI). Nicolson et al. (1996) further teach the symptoms of Chronic Fatigue Syndrome (CFS) and GWI are almost an identical match and that GWI is not a separate syndrome from CFS (p. 71). Specifically, Nicolson et al. (1996) use mycoplasma-specific probes derived from *M. fermentans, M. genitalium*, and *M. orale* in an assay which simultaneously detects the presence of these organisms in a sample via a Southern hybridization assay (p. 72). Nicolson et al. (1996) detected mycoplasmal infections in the leukocytes of 14 out of 30 patients with GWI, and approximately 65% of the patients had only *M. fermentans* infections (p. 74). Nicolson et al. (1996) refer to *M. fermentans* and *M. penetrans* as "pathogenic, invasive mycoplasmas" (p. 74), and suggest the development of diagnostic tests which employ the PCR amplification of invasive mycoplasmas for the detection of GWI (p. 77). Thus, Nicolson et al. teach a method which comprises the steps of isolating PBMC from an individual and detecting the presence of at least on mycoplasma species in said PBMC, wherein the presence of at least one of said species indicates an increased likelihood of the presence of CFS.

13. Claims 1-3, 5, 10, and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by Nicolson et al. (Biomedical Therapy, Vol. XVI, No. 4, October 1998).

Nicolson et al. (1998) teach a method for the detection of mycoplasma in the PMBC of patients known to have fibromyalgia syndrome (FMS) and/or chronic fatigue syndrome (CFS) using the polymerase chain reaction. Specifically, Nicolson et al. (1998) teach amplification of mycoplasma nucleic acids using genus primers specific and also the specific amplification of *M. fermentans* using species specific primers (p. 267-268). Following PCR amplification, Nicolson et al. (1998) teach a further step of using southern hybridization (p. 268). Nicolson et al. (1998) detected mycoplasma in 62.9% percent of patients with CFS/FMS, and in only 9% of healthy patients. *M. fermentans* was detected in 50% of the CFS/FMS patients and none of the healthy patients. Since the genus specific primers gave positive results in more samples than the primers specific for *M. fermentans*, it is clear that the genus specific primers were simultaneously detecting more than one species of mycoplasma. Thus, Nicolson et al. teach a method which comprises the steps of isolating PBMC from an individual and detecting the presence of at least on mycoplasma species in said PBMC, wherein the presence of at least one of said species indicates an increased likelihood of the presence of CFS.

With regard to claim 11, Nicolson et al. (1998) teach that cell penetrating mycoplasma species such as *M. fermentans* and *M. penetrans* can cause acute and chronic illness (p. 269), it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method described by Nicolson et al. (1998) to also include the detection of *M. penetrans* in order to create a test which determines an increased likelihood of the presence of CFS and/or FMS for the purpose of achieving a rapid diagnosis of CFS and/or FMS.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Choppa et al. in view of Nicolson et al. (International Journal of Occupational Medicine, Immunology, and Toxicology, Vol. 5, No. 1, 1996)

Choppa et al. teach a method which uses mutliplex PCR for the detection of *Mycoplasma fermentans*, *M. hominis* and *M. penetrans* in peripheral blood mononuclear cells of patients with chronic fatigue syndrome (see methods p. 302). Choppa et al. report that mycoplasmas were found at a significantly higher rate in CFS individuals over healthy controls (p. 307). Further, Choppa et al. suggest that such a detection technique would have a diagnostic value since there is a need for rapid reliable diagnostic procedures (p. 307). Thus, Choppa teach a method which comprises the steps of isolating PBMC from an individual and detecting the presence of at least on mycoplasma species in said PBMC, wherein the presence of at least on of said species indicates an increased likelihood of the presence of CFS.

Choppa et al. teach the detection of PCR amplification products by gel electrophoresis followed by ethidium bromide staining (p. 304), but they do not teach detection by Southern blot hybridization.

Nicolson et al. (1996) teach detecting PCR amplified products by Southern blotting (see Figure1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Choppa et al. to include the Southern blotting step as described in Nicolson et al. (1996) to create a method for the detection of mycoplasma with the expected benefit of providing an alternative means for detection of mycoplasma nucleic acids in a sample.

16. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vojdani et al. in view of Roll.

Vojadani et al. teach a method which employs a set of genus specific primers to detect mycoplasma in the PMBC samples of patients with CFS. Vojdani et al. further teach a method which uses PCR for the detection of *M. fermentans* in peripheral blood mononuclear cells of patients with chronic fatigue syndrome. *M. fermentans* was observed in 34% of patients with CFS as opposed to 8% of the control group (Table 1). Vojadani et al. observe that some samples were positive for mycoplasma genus but not for *M. fermentans*, indicating the detection of more than one mycoplasma species. Thus, Vojadani et al. teach a method which comprises the steps of isolating PBMC from an individual and detecting the presence of at least on mycoplasma species in said PBMC, wherein the presence of at least one of said species indicates an increased likelihood of the presence of CFS.

Vojdani et al. do not teach the use of mulitplex PCR in the specific detection of mycoplasma species in the PMBC of patients with CFS.

Roll teaches that multiplex PCR provides "specific sensitive and distinguishable simultaneous amplification" of organisms, and teaches that multiplex PCR provides significant advantages over single PCR methods in which one gene sequence is amplified (col. 15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Vojdani et al. to include multiplex PCR for the purpose of developing a quick, reliable and less expensive diagnostic technique for simultaneously detecting *M. fermentans* and other mycoplasma species as an indicator of an increased likelihood of having chronic fatigue syndrome.

17. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolson et al. (1996).

Nicolson et al. (1996) teach a method for detecting mycoplasma in the leukocytes of patients with Gulf War Illness (GWI). Nicolson et al. (1996) further teach the symptoms of Chronic Fatigue Syndrome (CFS) and GWI are almost an identical match and that GWI is not a separate syndrome from CFS (p. 71). Specifically, Nicolson et al. (1996) use mycoplasma-specific probes derived from *M. fermentans, M. genitalium*, and *M. orale* in an assay which simultaneously detects the presence of these organisms in a sample via a Southern hybridization assay (p. 72). Nicolson et al. (1996) detected mycoplasmal infections in the leukocytes of 14 out of 30 patients with GWI, and approximately 65% of the patients had only *M. fermentans* infections (p. 74). Nicolson et al. (1996) refer to *M. fermentans* and *M. penetrans* as "pathogenic, invasive mycoplasmas" (p. 74), and suggest the development of diagnostic tests which employ the PCR amplification of invasive mycoplasmas for the detection of GWI (p. 77).

Thus, Nicolson et al. teach a method which comprises the steps of isolating PBMC from an individual and detecting the presence of at least on mycoplasma species in said PBMC, wherein the presence of at least one of said species indicates an increased likelihood of the presence of CFS.

Nicolson et al. do not teach a method in which the two or more species are selected from the three species listed in claim 11. However, given that the teachings of Nicolson et al. (1996) include a method that employs the simultaneous detection of mycoplasma species, the teaching that *M. penetrans* is a "pathogenic, invasive mycoplasma," and the suggestion to develop diagnostic tests which employ the PCR amplification of invasive mycoplasmas for the detection of GWI (CFS) it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method described by Nicolson et al. (1996) to include the detection of *M. penetrans* in order to create a test which determines an increased likelihood of the presence of CFS for the purpose of achieving a rapid diagnosis of CFS.

18. Claim 11 rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolson et al. (Biomedical Therapy, Vol. XVI, No. 4, October 1998).

Nicolson et al. (1998) teach a method for the detection of mycoplasma in the PMBC of patients known to have fibromyalgia syndrome (FMS) and/or chronic fatigue syndrome (CFS) using the polymerase chain reaction. Specifically, Nicolson et al. (1998) teach amplification of mycoplasma nucleic acids using genus primers specific and also the specific amplification of *M. fermentans* using species specific primers (p. 267-268). Following PCR amplification, Nicolson et al. (1998) teach a further step of using southern hybridization (p. 268). Nicolson et al. (1998)

detected mycoplasma in 62.9% percent of patients with CFS/FMS, and in only 9% of healthy patients. *M. fermentans* was detected in 50% of the CFS/FMS patients and none of the healthy patients. Since the genus specific primers gave positive results in more samples than the primers specific for *M. fermentans*, it is clear that the genus specific primers were simultaneously detecting more than one species of mycoplasma. Thus, Nicolson et al. teach a method which comprises the steps of isolating PBMC from an individual and detecting the presence of at least on mycoplasma species in said PBMC, wherein the presence of at least one of said species indicates an increased likelihood of the presence of CFS.

Nicolson et al. do not teach a method in which the two or more species are selected from the three species listed in claim 11. However, in view of the fact that Nicolson et al. (1998) teach that cell penetrating mycoplasma species such as *M. fermentans* and *M. penetrans* can cause acute and chronic illness (p. 269), it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method described by Nicolson et al. (1998) to also include the detection of *M. penetrans* in order to create a test which determines an increased likelihood of the presence of CFS and/or FMS for the purpose of achieving a rapid diagnosis of CFS and/or FMS.

19. A. Claims 3, 6, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolson et al. (1996) in view of Hawkins et al. (The Journal of Infectious Diseases, 1992; 165:581-585) and

B. Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolson et al. (1998) in view of Hawkins et al.

Nicolson et al. (1996) teach a method for detecting mycoplasma in the leukocytes of patients with Gulf War Illness (GWI). Nicolson et al. (1996) further teach the symptoms of Chronic Fatigue Syndrome (CFS) and GWI are almost an identical match and that GWI is not a separate syndrome from CFS (p. 71). Specifically, Nicolson et al. (1996) use mycoplasma-specific probes derived from *M. fermentans, M. genitalium*, and *M. orale* in an assay which simultaneously detects the presence of these organisms in a sample via a Southern hybridization assay (p. 72). Nicolson et al. (1996) detected mycoplasmal infections in the leukocytes of 14 out of 30 patients with GWI, and approximately 65% of the patients had only *M. fermentans* infections (p. 74). Nicolson et al. (1996) refer to *M. fermentans* and *M. penetrans* as "pathogenic, invasive mycoplasmas" (p. 74), and suggest the development of diagnostic tests which employ the PCR amplification of invasive mycoplasmas for the detection of GWI (p. 77). Thus, Nicolson et al. teach a method which comprises the steps of isolating PBMC from an individual and detecting the presence of at least on mycoplasma species in said PBMC, wherein the presence of at least one of said species indicates an increased likelihood of the presence of CFS.

Nicolson et al. (1998) teach a method for the detection of mycoplasma in the PMBC of patients known to have fibromyalgia syndrome (FMS) and/or chronic fatigue syndrome (CFS) using the polymerase chain reaction. Specifically, Nicolson et al. (1998) teach amplification of mycoplasma nucleic acids using genus primers specific and also the specific amplification of *M. fermentans* using species specific primers (p. 267-268). Following PCR amplification, Nicolson et al. (1998) teach a further step of using southern hybridization (p. 268). Nicolson et al. (1998)

detected mycoplasma in 62.9% percent of patients with CFS/FMS, and in only 9% of healthy patients. *M. fermentans* was detected in 50% of the CFS/FMS patients and none of the healthy patients. Since the genus specific primers gave positive results in more samples than the primers specific for *M. fermentans*, it is clear that the genus specific primers were simultaneously detecting more than one species of mycoplasma. Thus, Nicolson et al. teach a method which comprises the steps of isolating PBMC from an individual and detecting the presence of at least on mycoplasma species in said PBMC, wherein the presence of at least one of said species indicates an increased likelihood of the presence of CFS.

With respect to claim 3, Nicolson et al. (1996) do not teach the detection of mycoplasma using PCR amplification. Hawkins et al. teach a method for detecting mycoplasma in a sample which employs PCR. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used PCR in a detection step for the detection of mycoplasma in the PMBC of CFS patients because PCR was known as an effective method for detecting nucleic acids in a sample, as exemplified by Hawkins et al.

With respect to claims 6 and 7, Nicolson et al. (1996) and Nicolson et al. (1998) do not teach the amplification of *M. fermentans* using primers consisting of instant SEQUENCE ID NO: 3 and 4. Hawkins et al. teach a method in which they amplify *M. fermentans* using primers consisting of instant SEQUENCE ID NO: 3 and SEQUENCE ID NO: 4 (p. 582) in AIDS patients. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the primers for the detection of *M. fermentans* disclosed by Hawkins et al. in the method taught by Nicolson et al. (1996) or the method taught by Nicolson et al. (1996)

to create an assay for the prediction of an increased likelihood of a patient having CFS or FMS for the purpose of a rapid and sensitive diagnostic technique.

20. A. Claims 3, 6, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolson et al. (1996) in view of Grau et al. (Molecular and Cellular Probes (1994) 8, 139-148) and

B. Claims 6 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolson et al. (1998) in view of Grau et al.

Nicolson et al. (1996) teach a method for detecting mycoplasma in the leukocytes of patients with Gulf War Illness (GWI). Nicolson et al. (1996) further teach the symptoms of Chronic Fatigue Syndrome (CFS) and GWI are almost an identical match and that GWI is not a separate syndrome from CFS (p. 71). Specifically, Nicolson et al. (1996) use mycoplasma-specific probes derived from *M. fermentans, M. genitalium*, and *M. orale* in an assay which simultaneously detects the presence of these organisms in a sample via a Southern hybridization assay (p. 72). Nicolson et al. (1996) detected mycoplasmal infections in the leukocytes of 14 out of 30 patients with GWI, and approximately 65% of the patients had only *M. fermentans* infections (p. 74). Nicolson et al. (1996) refer to *M. fermentans* and *M. penetrans* as "pathogenic, invasive mycoplasmas" (p. 74), and suggest the development of diagnostic tests which employ the PCR amplification of invasive mycoplasmas for the detection of GWI (p. 77). Thus, Nicolson et al. teach a method which comprises the steps of isolating PBMC from an individual and detecting the presence of at least on mycoplasma species in said PBMC, wherein

the presence of at least one of said species indicates an increased likelihood of the presence of CFS.

Nicolson et al. (1998) teach a method for the detection of mycoplasma in the PMBC of patients known to have fibromyalgia syndrome (FMS) and/or chronic fatigue syndrome (CFS) using the polymerase chain reaction. Specifically, Nicolson et al. (1998) teach amplification of mycoplasma nucleic acids using genus primers specific and also the specific amplification of *M. fermentans* using species specific primers (p. 267-268). Following PCR amplification, Nicolson et al. (1998) teach a further step of using southern hybridization (p. 268). Nicolson et al. (1998) detected mycoplasma in 62.9% percent of patients with CFS/FMS, and in only 9% of healthy patients. *M. fermentans* was detected in 50% of the CFS/FMS patients and none of the healthy patients. Since the genus specific primers gave positive results in more samples than the primers specific for *M. fermentans*, it is clear that the genus specific primers were simultaneously detecting more than one species of mycoplasma. Thus, Nicolson et al. teach a method which comprises the steps of isolating PBMC from an individual and detecting the presence of at least on mycoplasma species in said PBMC, wherein the presence of at least one of said species indicates an increased likelihood of the presence of CFS.

With respect to claim 3, Nicolson et al. (1996) do not teach the detection of mycoplasma using PCR amplification. Grau et al. teach a method for detecting mycoplasma in a sample which employs PCR. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used PCR in a detection step for the detection of mycoplasma in

the PMBC of CFS because PCR was known as an effective method for detecting nucleic acids in a sample, as exemplified by Grau et al.

With respect to claims 6 and 7, Nicolson et al. (1996) and Nicolson et al. (1998) do not teach the detection of *M. penetrans* using primers consisting of instant SEQUENCE ID NO: 7 and SEQUENCE ID NO: 8. Grau et al. teach the amplification of mycoplasma by PCR using the primers disclosed as instant SEQUENCE ID NO: 7 and SEQUENCE ID NO: 8 for the specific amplification of *M. penetrans* (Table 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nicolson et al. (1996) or Nicolson et al. (1998) by using the primers disclosed by Grau et al. for the detection of *M. penetrans* in order to provide a quick and reliable assay useful for the prediction of an increased likelihood of having CFS and/or FMS since Nicolson et al. (1996) suggest the detection the presence of *M. penetrans* as a means for the diagnosis of CFS in patients, and Nicolson et al. (1998) include *M. penetrans* in the group of cell-penetrating mycoplasma species which can cause chronic illnesses such as CFS and FMS.

21. A. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolson et al. (1996) in view of Roll (US 5627275).

B. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolson et al. (1998) in view of Roll.

Nicolson et al. (1996) teach a method for detecting mycoplasma in the leukocytes of patients with Gulf War Illness (GWI). Nicolson et al. (1996) further teach the symptoms of Chronic Fatigue Syndrome (CFS) and GWI are almost an identical match and that GWI is not a

separate syndrome from CFS (p. 71). Specifically, Nicolson et al. (1996) use mycoplasma-specific probes derived from *M. fermentans, M. genitalium*, and *M. orale* in an assay which simultaneously detects the presence of these organisms in a sample via a Southern hybridization assay (p. 72). Nicolson et al. (1996) detected mycoplasmal infections in the leukocytes of 14 out of 30 patients with GWI, and approximately 65% of the patients had only *M. fermentans* infections (p. 74). Nicolson et al. (1996) refer to *M. fermentans* and *M. penetrans* as "pathogenic, invasive mycoplasmas" (p. 74), and suggest the development of diagnostic tests which employ the PCR amplification of invasive mycoplasmas for the detection of GWI (p. 77). Thus, Nicolson et al. teach a method which comprises the steps of isolating PBMC from an individual and detecting the presence of at least on mycoplasma species in said PBMC, wherein the presence of at least one of said species indicates an increased likelihood of the presence of CFS.

Nicolson et al. (1998) teach a method for the detection of mycoplasma in the PMBC of patients known to have fibromyalgia syndrome (FMS) and/or chronic fatigue syndrome (CFS) using the polymerase chain reaction. Specifically, Nicolson et al. (1998) teach amplification of mycoplasma nucleic acids using genus primers specific and also the specific amplification of *M. fermentans* using species specific primers (p. 267-268). Following PCR amplification, Nicolson et al. (1998) teach a further step of using southern hybridization (p. 268). Nicolson et al. (1998) detected mycoplasma in 62.9% percent of patients with CFS/FMS, and in only 9% of healthy patients. *M. fermentans* was detected in 50% of the CFS/FMS patients and none of the healthy patients. Since the genus specific primers gave positive results in more samples than the primers

specific for *M. fermentans*, it is clear that the genus specific primers were simultaneously detecting more than one species of mycoplasma. Thus, Nicolson et al. teach a method which comprises the steps of isolating PBMC from an individual and detecting the presence of at least on mycoplasma species in said PBMC, wherein the presence of at least one of said species indicates an increased likelihood of the presence of CFS.

Nicolson et al. (1996) and Nicolson et al. (1998) do not teach the use of multiplex PCR for the simultaneous detection of two or more mycoplasma species.

Roll teaches that multiplex PCR provides "specific sensitive and distinguishable simultaneous amplification" of organisms, and teaches that multiplex PCR provides significant advantages over single PCR methods in which one gene sequence is amplified (col. 15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nicolson et al. (1996) or the method of Nicolson et al. (1998) to include multiplex PCR for the purpose of developing a quick, reliable and less expensive diagnostic technique for simultaneously detecting *M. fermentans* and other mycoplasma species as an indicator of an increased likelihood of having chronic fatigue syndrome.

Conclusion

22. No claims are allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The

examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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